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A Consideration of the Continued Fevers in the Tropics

A Dissertation.

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Introduction.

In the early days of Medical Science various names were given to a disease which is now recognized to be typhoid or enteric fever. To this malady the older French writers applied the name fievre typhoide. Petit and Serres described these fevers in the year 1813 as entero-mesenteric. This term entero-mesenteric had the advantage of marking the peculiar lesion of the disease. Bretonneau called the condition dothioenteric fever because of ~~the~~ a supposed pustular inflammation of the intestine. Cruveilhier and others have applied to it the name follicular enteritis. By the Germans it is commonly called typhus abdominalis. In America the name typhoid fever is the name of common usage. The description of these fevers given by clinicians in various countries is practically identical. It must be remembered, however, that only those cases with more or less pronounced clinical symptoms were considered to be typhoid fever in the early part of the last century. It may be well to emphasize the identity of the continued fevers in the United States with the typhoid fever described by the French pathologists. This seems to be clearly and positively established. No one familiar with the disease in Paris and so beautifully described by Louis, Chomel and Andral, and who has read Nathan Smith's

description of typhoid fever of New England can doubt ~~that~~ for a moment, so far as the symptomatology is concerned, that these fevers are identical. The identity of the infection in Europe and America from the pathological standpoint was established clearly by Dr. E. Hale, Jr. of Boston, who published in the Medical Magazine for December 18~~6~~33, an account of three dissections of persons considered by him to have died of typhoid fever. If the diagnosis in these cases can be looked upon as certain and positive, this account constitutes, so far as I know, the first published description of the intestinal lesion of the disease as it occurs in America. The diagnosis in all three cases must be regarded as somewhat doubtful, however, since the intestinal ulceration did not seem to have been very clearly or strongly marked. The first authentic and unquestionable cases on record are two which were published by Dr. Gerhard in the American Journal of the Medical Sciences for February 1835. Also in the Medical Magazine for June 1835. Bartlett gave a short account of the entero-mesenteric lesions in five cases of typhoid fever, these lesions corresponding exactly to those described by Louis. Previously, however, Dr. James Jackson, Jr. had observed the intestinal changes in a case of the disease in October 1830. Dr Jackson also made a study of

typhoid fever in Paris under the direction of Louis. Upon his return to America, he gave an account, in 1835, of two other cases in which he found characteristic lesions of the intestinal follicles and mesenteric glands. The report of Dr. Jackson states that the alteration of the Peyer's patches had been noticed at the Massachusetts General Hospital previous to 1833. Following these observations, more extensive and accurate studies were made by Drs. J. Jackson, Bigelow, Bowditch, Shattuck, Jr., Holmes, Hall, of Boston, and by Gerhard and Stewardson of Philadelphia, who have uniformly confirmed the early conclusions and demonstrated the identity of the typhoid fever of Paris with that of the United States. Other lesions were also described. According to Dr. Bartlett, for instance, the most frequent alteration in the character of the blood consisted in the diminution of the amount of its fibrin. In some cases he stated that the cavities of the heart, especially the right, contained fibrinous concretions of a whitish or yellowish color, but more commonly the blood was in the form of a dark coagulum or was entirely fluid. Many other interesting observations were made at this time. Chomel stated that all lesions of the disease finally disappeared in individuals who had had it and recovered. He said that in the numerous autopsies at the Hotel Dieu in Paris in many of which there were

good reason to think, that the subject had had typhoid fever, he never found any old cicatrices.

It is very interesting to read the statements of the earlier writers concerning the ways and means by which typhoid fever may be transmitted, and it is surprising to note, how well some of these earlier observations correspond with the views of the present day. In the earlier thirties M. Gendron stated that he believed the disease was transmitted by direct and repeated contact and by the presence of the sick without contact. He thought that it might be carried from a sick person to a well person, and communicated from individual to individual by a third who did not have the disease and also that it might be contracted by exposure to infected clothing, beds and similar fomites. He regards the first mentioned mode of transmission of the disease from one individual to another as the most common. The transmission by a healthy man he thought did not often happen, except in times of great epidemics. The disease was most frequently communicated, according to Gendron, to those who are in closest and most constant relation to the sick, i.e. nurses and attendants.

Typhoid Fever.

Enteric fever manifests itself in at least three different types, and each of these types is quite distinctly

defined. The sporadic form makes its appearance in cases more or less isolated, and occurring at different intervals without any apparent connection with other cases--the disease being totally absent from a given locality for a long period of time. Then sudden violent outbreaks occur which seem to be derived from a simultaneously acting agency affecting an entire community with common and fairly equal force, taking toll of the susceptible individuals in proportion to the extent of its operation in time and place. In addition to these two types or forms of enteric fever a third demands much careful attention. This third form is a modification as well as a combination of the two preceding forms. It assumes the character of small group outbreaks having a common origin, originating from a central focus, giving rise to isolated cases at intervals which oftentimes appear to link up or connect the group outbreaks. These intervals quite often correspond to the ordinary period of incubation.

Enteric fever has for a long time been recognised in all habitable parts of the world and under almost all sorts of climatic conditions. No region occupied by man has been found capable of conferring immunity. Still within the same locality we find extreme contrasts in epidemics occurring in different places at the same time

or in the same places at different times. No fact is more clearly established than the definite relation of the seasons to the occurrence of enteric fever. This is especially true in the endemic areas, but characteristic variations are shown in different latitudes. There are then certain prominent features commonly seen in the epidemiology of enteric fever, in relation to the human host, both as regards place or locality and the age and sex of the individuals attacked. The disease seems to have a marked preference for certain areas where its occurrence may be expected at any time, regardlessof climatic restrictions. Just how much value should be attached to race immunity or race susceptibility is very difficult to say. In certain outbreaks of the disease it has been observed that some races are more prone to enteric fever than others. Again in certain localities the age of the individual seems to play a considerable role in the epidemiology. All of these conditions presuppose some well established cause or factor which must be the underlying basis. The advent of bacteriology in the field of medicine showed that one particular strain of microorganisms was associated with enteric fever. Until within recent years the typhoid bacillus discovered by Eberth in 1884 was thought to be the only etiological factor in the disease, but as the study of these cases became

more widespread, other organisms were isolated from typhoid-like cases, until at the present time it is accepted that clinical enteric fever may be caused by several different organisms. These organisms possess cultural characteristics sufficiently distinctive to make their separation one from the other comparatively simple. Various observers have demonstrated the fact that these organisms are widely distributed in the human body during the disease, carried to the various organs and tissues by the blood and lymphatics. They can be easily demonstrated in the blood during life early in the course of the disease by proper methods. In typhoid and closely allied fevers the organisms are present in the urine in from twenty to thirty percent. of all cases and von Drigalski, Conradi and others claim to have isolated them from the stools in practically all cases of continued fever at some time during the disease. At autopsy the bacilli are found in all of the organs of the body and are most numerous in the spleen, mesenteric glands, gall bladder, while they may be found in the muscles, uterus and lungs.

After carefully studying the various conditions associated with enteric fever such as locality, races of individuals, climatic distribution and the etiological agents, the writer became convinced that the most important question to be considered was how these infections

are carried into so many different parts of the world, under so many different conditions: First of all enteric fever is an intestinal disease with a specific affinity for the intestinal tract of man. Since these organisms have a specific fondness for the intestinal tract, how do they find their way into this structure? Among the common carriers of the disease must be mentioned water, food stuffs, raw vegetables, uncooked meats, oysters, sea foods of various sorts and milk. These are the principle sources of infection. There are probably others which play a considerable part in the causation of typhoid and typhoid like diseases. Granting that all of these agencies may be important in an epidemic and that certain bacteria are the only etiological factors concerned we are brought to the question of explaining the contact which takes place between the human host and the bacteria. In other words, we have the human host and the infecting organism in the struggle of existence. The disease process can then be expressed as the result of the constituent factors. The outcome is prefigured in the varying structures and qualities of the human host, from which there emerges a certain definite reaction. Symptoms then are set up in response to the stimulation of the invading bacteria under the influence of varying conditions. Perhaps in this fact lies the explanation of the wide

range in the pathogenic results due to the varying reaction of the tissue cell and the stimuli. In the life history of unicellular organisms nutrition and the propagation of the species may be considered as a correlated function. The struggle for life is the sole determining factor and both tissue cells and bacterium are prolific under favorable conditions and subject alike to the laws of heredity and variation. The recent work on the relation of organisms of one species to the cells of another species and the production by the latter of specific antibodies will serve to illustrate the likeness of these unicellular bacteria and tissue cells. Both bacterial cells and tissue cells conform to the general laws of evolution, each modified by variation and environment. Whether or not disease or immunity is the final result of the struggle between the two depends entirely upon which of these active forces has the greater attack and defensive power and the triumph of one over the other determines the final result

Paratyphoid fever.

Paratyphoid fever is an acute infectious disease caused by an organism related to the typhoid bacillus and resembling true typhoid fever so closely that it is difficult

to separate from fevers due to the typhoid bacillus. So varied indeed are the clinical symptoms of typhoid fever that it is manifestly impossible to say that this case of fever because it is more mild and lacks many of the classical symptoms of the disease belongs to the paratyphoid group. In other words, there exists no uniform definite clinical standard of symptoms whereby we can say that this or that case of fever is due to the reaction of this or that bacillus. The real solution of the question as to what constitutes the paratyphoid fever group is due more to the Widal reaction than to any other one phenomenon. This reaction was first described by the French physician Widal on the basis of the discovery of the agglutins by Gruber and Durham. It may be said to have started the inquiry into the intricate nature of enteric fever. Like all new reactions which are likely to lend service to clinical diagnosis, the Widal reaction was much studied and greater claims for it were made than its true value deserved. It was at first only natural to put aside a diagnosis of typhoid fever if the Widal reaction was found to be negative. Later on it was observed that typhoid bacilli were not the only organisms capable of being agglutinated by a typhoid-immune serum. It was also observed that some individuals in perfect health and

who have never been ill gave the Widal reaction. All of these observations came to light even before the days of blood cultures.

The term paratyphoid fever was first used in 1896 by Achard and Bensuade for infections in which they had isolated from the urine an organism quite like but not identical with the typhoid bacillus. In the following year Widal, and later Widal and Nobecourt isolated from a neck abscess an organism apparently identical with the one previously isolated from the urine. Gilbert speaking of these cases of Widal and Nobecourt described these infections as paratyphoid infections, because they seemed to be caused by an organism related to the typhoid bacillus. In the following year 1898 Gwyn succeeded in isolating from the blood of a case whose clinical symptoms were similar to those of typhoid fever, a bacillus he called the paracolon bacillus because of its resemblance to Bacillus coli. This bacillus was agglutinated by the patient's serum while the typhoid bacillus was not affected. Schottmüller in 1900 isolated a similar bacillus from the blood of six cases whose clinical symptoms were similar to those of typhoid fever. Schottmüller recognised differences existing among these so-called paratyphoid bacilli and later, Brion and Kayser pointed out characteristic distinctions in the cultural reactions of these

organisms. Kayser designated one of these strains as paratyphoid bacillus type A, and another as type B. This latter organism owing to its frequent occurrence in typhoid like cases and on account of its relation to the hog cholera group has been given during the past few years considerable attention. The Brion Kayser type A has however been seldom found as a cause of typhoid like diseases. Cases of enteric fever have been described by Gwyn, Cushing, Coleman and Buxton, Johnson, Hewlett, Hume and Schottmüller where the paratyphoid bacilli type A have been isolated. The first communication relating to the isolation of such bacilli from the intestinal contents is given by Kurth. From time to time various workers have devised methods for the isolation of organisms from the stools of patients ill from typhoid fever. In the first great paratyphoid epidemic which occurred in Saarbrücken in an investigation of the stools of thirty-eight patients the paratyphoid bacilli were recovered eighteen times. This epidemic has the distinction of being the first where fairly accurate bacteriological methods were used for the detection of the paratyphoid bacilli. De Brion and Kayser in the small epidemic of fourteen cases in Eibrugen, Holland, were not able to isolate the organisms. The diagnosis was made on the result of the Widal reaction for paratyphoid bacillus type B. The

nine cases reported by Lupnik and Posner were based for the most part on the agglutination test. From only two cases could paratyphoid bacilli be isolated from the feces. Lentz by the use of Loeffler's malachite green medium succeeded in isolating these organisms from the stools of fifty-one cases. Lembke in his description of the paratyphoid epidemic in Lobenheim states, that the diagnosis of paratyphoid fevers was made solely on the results of the Widal reaction. B.Fischer made stool examinations in forty-two cases and found the organisms present in thirty-eight cases, Conradi, v. Drigalski and Jürgen's investigation of the Saarbrücken epidemic demonstrated that these organisms can be isolated from stools of paratyphoid cases from two to nine months after convalescence. Lentz afterwards stated that there were cases which harbored in their stools both the typhoid and paratyphoid bacilli for a much longer time than nine months and he described these individuals as typhoid carriers. It was further pointed out by Conradi, v. Drigalski and Jürgens, that healthy individuals who have been in contact with enteric fever patients might harbor these same organisms in their intestinal tract and thus be typhoid carriers. Achard and Bensuade, Furth, Conradi, v. Drigalski, Jürgens, B. Fischer, Kutscher and Lane observed paratyphoid bacilli

in the urine during the course of the disease and likewise during convalescence. The isolation of these organisms both from the feces and urine of patients ill from these enteric fevers is in all cases a most valuable aid in the diagnosis. Still before these organisms can be considered to be the true etiological factor of these fevers, they must either be isolated from the blood or glands of the patient during life or from the organs after death. One or both of these requirements is absolutely necessary before we are justified in concluding that this or that organism has been the cause of the disease. From the clinical standpoint it may be said that it is necessary to isolate these different bacilli from the blood during life before a correct diagnosis can be made. In the first place the blood under normal conditions is free from bacilli and when organisms are isolated under the strictest precautions and in pure culture, the organism so isolated must be considered as standing in etiological relationship to infection. In the feces we find a rich bacterial flora and even with special media it is difficult not only to isolate organisms of the intermediate group, but difficult even then to say whether or not they have played any real part in the causation of the patient's illness. So we must regard the isolation of the organism from the blood as the only means of revealing the true

cause of the fever. Among the first investigators to isolate from the blood of enteric fever cases, bacilli of the par·typhosus group type B may be mentioned Schottmüller, Korte, Jochman and Rolly, Brion and Kayser. The three cases described by Ruediger as well as the one described by Smith were very probably members of this same group. Brill isolated an organism from the splenic blood of an enteric fever case. While his descriptions are not exactly clear, the probabilities are that this bacillus is a member of the paratyphoid group type B. The members of the paratyphoid group occur in the blood and various organs and tissues under the same conditions as do the typhoid bacilli and it is doubtless true that they are distributed in nature in the same way and gain entrance to the human body in the same manner as do the other organisms. They are present in the blood in the same period of the disease as are the typhoid bacilli and seem to persist in the blood for a similar length of time. They seem to remain in the feces and urine for an equal period. All of the early investigators including Schottmüller, Korte, Rolly, Brion and Kayser, Conradi, v. Drigalski and Jürgens, with but one exception isolated the organisms from the blood of their cases, on or before the fifteenth day of the disease. According to the observations of Pratt, Forster and Kayser the paratyphoid species seems

to have a predilection for the gall bladder. Pratt and Fischer were apparently the first in America to isolate the paratyphoid bacillus from abscesses occurring in cases having typhoid-like symptoms. Fischer states that he isolated the paratyphoid bacillus from a local infection in a paratyphoid case. At autopsy the bacilli are easily isolated and among the first to isolate them from the various organs, tissues and secretions may be mentioned Lucksch, Vagedes, Brion and Kayser.

The paratyphoid bacillus type A as a disease producer seems to play only a subordinate part in human pathology, although cases have been described by various workers. The organisms stand in close relation to the paratyphosus bacillus type B and to the typhoid bacillus. This paratyphosus type A grows on all weak alkaline medium precisely like the typhoid bacillus, but differs in that it forms gas in glucose. It is differentiated from paratyphoid B in that it produces less gas in this medium. It does not coagulate milk which at first remains unchanged, while it later becomes permanently acid. Paratyphoid type B is first acid then alkaline in litmus milk. The paratyphoid bacilli types A and B are pathogenic for guinea pigs and white mice and both produce a general infection with more or less marked enteritis and hemorrhages.

The infection of man with the paratyphoid bacillus

give rise to specific antibodies. The serum during the course of the disease and during convalescence is more or less specific for one type. According to Gwyn, Cushing, Coleman and Buxton, Brion and Kayser paratyphoid bacilli and typhoid bacilli produce both specific and group agglutines.

Enteric Fever in Panama

We know very little of the early history of enteric fever in the republic of Panama before the influx of Americans during the earlier construction period, for the reason that typhoid and in fact nearly all cases of fever, until within recent years were thought to be malaria. This was due in part to the fact that ~~almost every~~ many cases of typhoid were complicated with a malarial infection. Then too physicians had no means of accurately separating these enteric fevers from malaria, except those cases which ran a long continued course, and were clearly typhoid fever. Whether or not the disease was found on the Isthmus of Panama prior to 1904 is uncertain since we have no accurate case records. Still it is quite natural to believe that the travel of the Panamanians to and from the United States and European countries must have introduced a few cases of enteric fever from time to time. It is however doubtful if it got much of

a foothold until after the beginning of the work on the canal. Very little was known as to the prevalence of enteric fever prior to 1907 at which time the writer began a systematic study of continued fevers in the various hospitals and sick camps.

The sanitary conditions in vogue all over the republic of Panama and more especially in the cities and villages within the boundaries of the canal zone and including the cities of Colon and Panama were then in the most primative condition imaginable. The most important epidemiological factors of intestinal infections are mentioned below.

Epidemiological Factors.

Water. Public water supplies had to be provided the inhabitants of Panama by the Americans. The water originally came from open rain barrels, cisterns or private wells. The Americans with their absolute sanitary control of the canal zone set to work to improve the supply. The sanitary department of the Isthmian Canal Commission attempted to provide pure water, not only for the employees of the canal zone, but also for the cities Colon and Panama. The new water was obtained from large catch basins or water sheds and delivered to the people directly. The difficulty of maintaining these water sheds free from pollution led to the installation of

condensers at various places and water thus obtained was distributed to the Americans and others employed on the canal zone. Later on all the water used was purified by mechanical filtration. Much of the enteric fever with which we are concerned occurred before the complete installation of these filter plants.

The distribution of water from reservoirs or from condensers to the individual consumer without its becoming more or less polluted is in itself a problem of some little importance. As a practical procedure water was distributed to the whites from the water mains or else the condensed water was supplied them in large bottles or demijohns. The water was furnished the foreign and colored employees in square oil cans the tops of which had been removed, pieces of wood nailed across the tops of these cans serving as handles. These cans held about five gallons. The carrier's hands would necessarily come in contact with the water and easily contaminate it.

Flies

Perhaps the greatest distributing agent of enteric fever in Panama was the domestic fly, and this is especially important when we consider the commission eating places (I.C.C. Hotels). These Isthmian Canal Commission hotels and restaurants were for the most part well screened.

Still it is a difficult task to keep out flies especially where they are so abundant as in a tropical country. Here native servants must be depended upon and to impress upon them the importance of cleanliness and proper screening is a difficult task. It is indeed almost impossible to enforce those strict sanitary requirements which are necessary to protect both raw and cooked foods from contamination.

Milk and Green Vegetables.

The milk supply of the Canal Zone can be omitted from the list of causes of enteric fever owing to its limited use and strict supervision. For a similar reason the supply of green vegetables played little if any part in the spread of the disease. There are many vegetables purchased in the open market, which are grown chiefly in Chinese gardens, but since no artificial fertilization is made use of this source might likewise be eliminated as a possible factor in enteric fever.

Ice Tea

A somewhat peculiar and slowly drawn out infection occurred in one of the Government Hotels located at Empire. Strict bacteriological investigation of the hotel foods and drinks, revealed the fact, that the

iced tea was probably the cause of the trouble. After the tea was prepared it was placed in open barrels, and larger pieces of ice were put in the barrel to cool the tea. The pitchers used in carrying the ice tea to the table were submerged in the barrel in the process of filling, and not infrequently the waiter's hands came in contact with the beverage -- and the tea therefore was open to contamination. The bacterial counts of the ice tea showed 1,500,000 bacteria per cubic centimeter. Bacillus coli was present in 1/250 of a c.c. This finding put an end to the use of the open barrels. As soon as the barrels were filled by funnels (through bunghole) in the tops and the tea drawn out by faucets from below the ice being placed in the individual glasses, and the barrels protected from flies, no more cases of enteric fever were reported from these hotels.

Artificial Drinks

Another source of infection or distributing agent of enteric fever which has never received its due share of consideration, and one which I am convinced has played an important role in the Isthmus of Panama, is the use of various soft drinks, such as coco-cola, ginger-ale, orangeade, champaigne cider, and other sodas of various flavors. The bottling companies supplying these drinks going under various names, in almost every instance, made

use of bottles collected from garbage carts and in fact wherever they could be obtained. These bottles were washed twice in cold water, and left to partially dry, without boiling or any other attempt at sterilisation. The syrup and water were put in the bottle and charged with CO_2. The water that was used was in most instances open to grave chances of pollution. The whole manufacturing process was carried on in some poorly constructed shack, apparently without the slightest intention of conforming to any sanitary requirements. The lack of regard for the proper sanitary measures was revealed in the bacteriological findings of the products purchased in the open market. These sodas almost invariably showed an excessively high bacterial count, and the fermentation tests revealed the presence of fermenting bacteria in dilutions as high as 1/250 of a c.c. Later confirmatory tests proved that these organisms belong to the bacillus coli group. It would, of course, be difficult to trace any definite number of cases to the drinking of these sodas, still the sanitary surroundings under which these beverages were prepared and the fact that upon examination they showed evidence of gross pollution, make it seem quite evident that they may have been a contributing factor in the spread of enteric fever.

Clinical and Bacteriological Observations

It has been observed for some time that many of the continued fevers in Panama do not conform to the type of fever usually known as typhoid and which is caused by the typhoid bacillus. It has been noted that the postmortem findings in a number of these fatal cases revealed lesions somewhat suggestive of septicaemia. These findings led to the examination of the various hospital records on the Isthmus of Panama, and more especially those of Ancon Hospital. The writer was at once struck by the frequent appearance of cases which for the want of a better diagnosis were called "fevers of an undetermined origin." These cases were quite often fatal and in most instances were characterised by a low grade of fever and clinical symptoms not so very unlike those shown in a typhoid infection.

These observations led to an inquiry into the nature and causation of these fevers. This investigation was divided into two parts, a clinical analysis of the symptoms, and a bacteriological study and classification of the cases into group corresponding to the organisms found in the patient's blood. My attention was not only directed to those cases of fever which are easily recognised clinically as typhoid, but, in addition, to those admitted to the hospital with a slight rise of temperature, cases in which the diagnosis was more or less obscure. Systematic

routine blood cultures were therefore made on all cases of fever admitted to the hospitals.

This investigation of tropical fevers covers a period of a little more than two years' work and during this interval 1185 blood cultures were made. This number does not represent 1185 individual cases of continued fevers, since in many instances at least three or more blood cultures were made on the same patient during the course of illness. I wish to consider in this paper the study of 108 cases of continued fevers in which specific organisms were isolated from the blood.

In the earlier part of the investigation various kinds of media were used for the isolation of the organisms. After making a comparison of the media used by other workers it was decided to use a bile glycerin combination which was found to yield most satisfactory results. It is essentially the same as that described by other workers. Ox-bile was obtained from the slaughter house, filtered and used with glycerin and peptone. The medium was made up in proportion of ox-bile 90 cc. peptone 10 grams, glycerin 10 cc. About 40 cc. of the mixture were placed in wide mouth bottles of about 100 cc. capacity and sterilised in the autoclave for 15 minutes at 15 pounds pressure. The syringes for blood cultures were the all glass Luer (American make) having a capacity of 10 cc. and

were also sterilised in the autoclave for 15 minutes at 15 pounds pressure. The patient's arm was thoroughly cleansed with soap, water and alcohol, after which procedure a bichloride dressing was applied. The needle of the syringe was inserted into the vein at the bend of the elbow and 10 cc. of blood aspirated and transferred immediately to the bile-glycerin medium which was then incubated 18 to 24 hours. If the first set of agar plates was sterile at the end of 24 or 48 hours then a second and even a third set of plates was poured from the original blood glycerin culture. In every instance where colonies appeared on the plain agar plates, five of these colonies were marked and studied. From each of these colonies two transfers were made, one to a plain agar stab, which was sealed and kept as a control culture, another to an agar slant which was used for subcultures. These included broth, milk, gelatin, potato, Dunham's solution and the following carbohydrates: glucose, lactose, saccharose, galactose, mannite, dextrin, sorbite, inulin, dulcite, maltose, levulose, arabinose, raffinose, mannose, zylose, rhamnose, and glycerin. These cultures were incubated at 37° and observed at intervals of 24 hours, five days and ten days except the gelatin and milk which were kept under observation for at least fifteen days. If at the end of fifteen days the milk was not

coagulated heat was applied to further determine its coagulability. The carbohydrates were used in a semisolid medium for the determination of acid and gas, the medium being made as follows: seven grams of agar, six grams of gelatin, ten grams of peptone and ten grams of the carbohydrate (Merk's C.P.), the volume being made up to 1,000 cc. and enough litmus solution added to give the medium a faint purple tinge. The mixture was sterilised in the autoclave for ten minutes at five pounds pressure. The organisms were also tested on the same media, sterilised with streaming steam in the Arnold steriliser, the results proving identical with those found with media sterilised in the autoclave. After the organisms were isolated from the patient, their blood serum was tested with these strains, for the specific agglutinins. Only those which were definitely agglutinated by the patient's serum were regarded as etiological factors in the production of the fevers.

Typhoid Fever

The number of cases admitted to the hospitals, from which positive blood cultures were obtained was 108. When we come to study the cultural characteristics of the organisms isolated from these cases, a remarkable result was found. Only 47 (43%) of these cases of continued fevers were true typhoid fever, i.e. caused by the typhoid bacillus. In these cases the cultural characteristics of the organisms isolated correspond in every detail to the reactions usually ascribed to the typhoid bacillus. These bacilli are of medium size and have round ends. They are actively motile, have peritrichic flagella,

and are Gram negative. Excellent bipolar stains are obtained when the organisms are grown on potato. The colonies on plain agar plates are medium sized, round, slightly raised, homogeneous, with a characteristic opalescent bluish gray appearance. On agar slants the growth is moist, opalescent, bluish gray. In gelatin stab culture the growth is abundant along the line of inoculation and on the surface spreads out as a thin bluish-gray covering.The gelatin is not liquefied. In broth the organisms grow with a slight diffuse cloudiness. Milk is not coagulated. At first no change is obeerved in litmus milk, but later the culture turns acid and remains acid.

On potato, as a rule, the growth is very characteristic. It covers the surface as a moist almost invisible layer. These bacilli do not split any of the carbohydrates with the formation of gas. Acid fermentation takes place, however, in glucose, galactose, mannite, maltose, levulose, raffinose, mannose, and zylose, but no acid fermentation is observed in lactose, saccharose, dextrine, sorbite, inulin, arabinose, rhamnose, salicin, or melanyte. These organisms do not produce indol. They were agglutinated by the patient's own serum and were pathogenic for guinea pigs.

Clinical Features.

In analysing these cases of true typhoid fever it must be remembered that a greater part of the fevers

under consideration occurred among the colored races and the histories submitted by the patients are very unreliable. Careful review of the temperature charts and a study of the symptomatology often showed an extremely short course of fever. From this it might be inferred that ambulatory cases were admitted during de~~f~~fervescence. Fortunately, however, a valuable check is given by the blood cultures which we know from the work of others give positive results only when taken during the first ten or twelve days of the disease. In reviewing the histories of these forty-seven cases which gave positive cultures of the typhoid bacillus we find that these cases conform to the symptom-complex usually described as true typhoid fever. About one-half the number occurred among Barbadian negroes; about 10% in Spaniards and the remainder among the various West Indians and Americans. Almost all of these cases were between the age of nineteen and thirty. While more cases occurred at Gatum than in any other locality, almost every town from Colon to Panama contributed one or more cases. Most of the patients complained of headache, fever, sore throat, pains in the stomach, vomiting and sometimes chills, cough and backaches. The clinical findings on admission were fairly constant, viz: furred tremulous, flabby tongue, enlarged liver and spleen, low tension pulse frequently dicrotic, tenderness just above and to the right of the umbilicus, diarrhoea or constipation, and in many instances albuminuria.

Duration of the Fever.

The duration of the fever was extremely variable ranging from two to four weeks, although a five and even a six weeks fever was not at all rare. As a rule, the fever was more or less continuous with slight remissions during the height of the disease (when blood cultures were positive) and became more or less remittent toward the end of the infection. The severity of the onset was no guide to the duration of the disease or to the development of complications.

In 7 of the 47 cases of typhoid fever, or 14.8% either recrudescence or definite relapse took place usually at about the time the temperature approached normal. In one case this reinfection occurred after the temperature had remained normal 13 days.

Nephritis.

Nephritis or degeneration of the renal epithelium was nearly always present in a more or less severe degree particularly in the negroes; in 31 cases studied in Ancon Hospital, nephritis was present in every one, and repeated examination during the course of the disease showed that it persisted in a more or less subacute or chronic form during convalescence in 78% of the cases. I am inclined to believe that typhoid toxaemia is one of the causes of the chronic nephritic conditions so often met with in typhoid fevers. The nephritis is

apparently of the chronic diffuse degenerative type. A similar nephritis occurs frequently in the course of severe malaria, and owing to the frequent malarial complications of typhoid fever it is possible that malarial toxins play some role in the causation of the nephritis of typhoid fever.

Postmortem Findings.

Seven of these 47 patients died, two from hemorrhage, one on the ninth day after admission, and the other on the ninth day of the relapse, and one from a complicating pneumonia which began about the end of the first week and proved fatal thirteen days afterwards. Of the remaining four fatal cases three had malarial infections on admission and one case developed a double suppurative parotitis.

Postmortem examinations were made on but three of the seven fatal cases, the two which died of hemorrhage and the one that died of complicating pneumonia being sectioned. The lesions found were very similar, hyperplastic or necrotic lymph nodes, hyperplastic or ulcerative Peyer's patches, acute splenic tumor, malarial pigmentation and cloudy swelling of all viscera. One case showed acute diffuse nephritis. Two cases showed focal necrosis in the liver and three, capillary bronchitis or bronchopneumonia. In the two cases which died from hemorrhage, ulcerative lesions of the intestine were present.

Paratyphoid Fever Type B.

In cases of enteric fever with clinical symptoms suggestive of typhoid fever the paratyphoid bacillus type B was isolated from the blood of 26 cases. These paratyphoid bacilli are to be characterised as medium sized rods, Gram negative, motile and as having peritrichic flagella which are easily stained even on very old cultures. The colonies on agar are round, homogeneous, raised and moist. By direct light they are opalescent and bluish gray. The growth on agar slants is abundant and by direct light is opalescent and bluish gray. In gelatin stab cultures the growth is abundant along the line of inoculation and the surface of the medium is covered with a moist, bluish gray growth. These organisms impart to broth cultures a light diffused cloudiness. Milk cultures are not coagulated. Litmus milk at first remains unchanged, but after three to five days it turns strongly alkaline. Later the organisms may even dissolve the casein and form numerous fat drops on the surface of the medium. The phenol and nitrate reactions are negative. The indol reaction is also negative. These bacilli form gas and acid in glucose, mannite, galactose, maltose, dextrine, sorbite and arabinose, but neither gas or acid fermentation occurs in lactose, saccharose, raffinose, sorbite, inulin or salicin. The patient's serum gave, as a rule, negative

Widal reactions for typhoid and paratyphoid, although the organisms isolated were usually agglutinated in rather high dilutions. These organisms are pathogenic for guinea pigs. These organisms were agglutinated by the patients own serum.

Clinical Features.

Since these organisms differed markedly from the typhoid bacillus it proved interesting to try and determine if they gave rise to a symptom complex sufficiently characteristic to be distinguished from true typhoid fever. This paratyphoid group was represented as stated above by twenty-six cases of continued fever. In all of these cases the nature of the onset was similar to that of true typhoid fever, but the symptoms were very much milder. The period of temperature while similar to that of the true disease, was, as a rule, several days shorter. There seemed to be a greater tendency to relapse than in typhoid fever. Twelve of the twenty-six cases showed either a relapse or recrudescence, about 46%. In this series of cases there were no hemorrhages or other symptoms of intestinal ulceration. The only complication was a ruptured spleen in one case. In this case a pure culture of paratyphoid bacillus B were isolated from the peritoneal cavity. In only two of these cases was there a marked nephritis. In one case aestivo-autumnal malarial parasites were present in the

patient's blood on admission and may account for the nephritis. One case died but unfortunately no postmortem examination was made. The Widal reaction was more frequently positive than in true typhoid fever, and the reaction occurred earlier than it did in the true typhoid cases. These paratyphoid fevers are moreover sharply distinguished from true typhoid fever in that there was a greater tendency to relapse or to recrudescence. The prognosis was always much more favorable.

Miscellaneous.

The remaining 35 cases of continued fever in my series of 108 were found to be infections with microorganisms distinct from either the typhoid or the paratyphoid bacilli. I have divided these other fevers into four sub-groups according to the cultural characters of the organisms obtained from the blood of the patients.

Continued Fevers Group A

This group embraced thirteen cases of continued fevers and is associated with an exceedingly interesting group of bacilli, which do not conform to the descriptions of either the paratyphoid or typhoid organisms. These bacilli are medium sized rods, motile, with peritrichic flagella and are Gram negative. The colonies on agar are round, moist, homogeneous, and by direct light have a

bluish gray appearance. The growth on agar slant is abundant and has a bluish gray appearance. The growth on gelatin stab is abundant along the line of inoculation. The surface growth is smooth resembling in appearance the growth on agar slants. Milk is not coagulated, and no acid or alkaline changes are observed in litmus milk. The growth in broth is not unlike that shown by paratyphoid and typhoid bacilli. The growth on potato is almost invisible during the first few days of incubation, later, however, the organisms produce a distinct growth resembling the surface of the potato in color. In some strains a faint trace of indol is observed. All of these bacilli produce gas and a slight amount of acid in glucose, mannite, saccharose, dextrine, sorbite and dulcite, but no gas or acid is noted in lactose, galactose, levulose, maltose, glycerin or inulin. Such organisms were isolated from 13 cases of continued fevers.

Clinical Symptoms.

The duration of the fever was about the same as that of true typhoid fever, and the temperature charts show a very irregular remittent type. There were no relapses or recrudescences in this group. Five of the 13 cases proved fatal, a mortality of about 38%. The autopsy findings in these cases were as follows:

Case 1. Subacute diffuse nephritis, anemia, general anasarca, cardiac dilatation, anemic infarct in spleen and hemorrhagic erosion of the stomach.

Case 2. Amoebic abscess of liver, ulcerative colitis (amoebic), oedema and congestion of the lungs, capillary bronchitis and acute degenerative nephritis.

Case 3. Gangrene of the left foot, thrombosis of the left iliac and femoral veins, multiple infarction of the kidneys, acute enteriaitis, mesenteric lymphadenitis, slight cardiac thrombosis (mural).

Case 4. Acute hemorrhagic nephritis, hemorrhagic bronchopneumonia, catarrhal gastritis and anemia.

The Widal reaction in this series of cases was negative throughout the course of the disease. This type of fever seems to be more serious than either the typhoid or paratyphoid fevers, and may be considered as the severest form of the continued fevers. These organisms were agglutinated by the patients serum.

Continued Fevers Group B.

A second group of organisms was isolated from the blood in six cases of continued fevers. The morphological characters of these organisms and the growths on agar, milk, broth, gelatin and potato correspond in every way to the reactions of the typhoid bacillus. On the various carbohydrates some very interesting differences are to be noted. The sugar reactions take place very slowly but after five days incubation both acid and gas are produced in

galactose, mannite, dextrine and dulcite. In addition to these changes acid fermentation is observed in glucose, lactose, saccharose, sorbite, levulose, maltose and glycerin.

Clinical Symptoms.

The temperature variations in these cases resembled somewhat those seen in true typhoid fever. The fever lasted usually 4 or 5 weeks. The fevers seem to be more irregular and more remittent than the types of fever just described. In this series of cases there were no complications, and nephritis played only a small role. One death occurred with the following postmortem findings: lymphatic hyperplasia with necrosis in the ileum, appendix, and colon, acute splenic tumor, acute bronchitis, catarrhal enteritis, cloudy swelling of the viscera, acute nephritis, ascariasis and uncinariasis.

The typhoid and paratyphoid Widals were negative in every case even as late as the 38th day of the disease.

Continued Fevers Group C.

A third interesting group of bacilli was found in eight cases of continued fevers. The cultural characters of the organism are quite distinct from those already described. In many ways they are closely related to bacillus coli. Morphologically they are not unlike the bacillus of Escherich. The colonies on agar plates, the growths on

agar slants, the growths in broth and in gelatin are identical with those of the colon bacillus. These organisms do not coagulate milk, neither do they produce any changes in litmus milk, even after long incubation. On potato at first the growth is almost invisible, but after five or six days, a faint lemon yellow growth is observed. Two of these strains gave a faint indol reaction, while the other strains were negative. None of these strains reduce nitrites to nitrates and no phenol is formed. This group of bacilli ferments the following carbohydrates with the formation of both gas and acid, glucose, lactose, galactose, mannite, dextrine, maltose, dulcite and sorbite. No changes are observed in saccharose or salicin. All the bacilli were agglutinated with the patient's own blood. All members of the group are pathogenic for guinea pigs. The fact that these organisms form both gas and acid in lactose media and do not coagulate or produce acid in milk is an anomoly not yet explained

Clinical Symptoms.

The cases of fever associated with these bacilli came from a single locality. The temperature curves in this group were not high with but one exception. The clinical symptoms of these cases were not unlike those of typhoid fever, One of these cases aborted on the eighth day of the disease. Another case developed a cardiac complication late in convalescence. The case with the highest temperature died, and the postmortem findings were as follows:

ulcerative enteritis, hyperplasia of the mesenteric lymph nodes, acute tubercular lymphadenitis, chronic proliferative pleuritis (left); incomplete rotation of the viscera (intestines); right bronchopneumonia. In one of these cases the Widal reactions for the typhoid and paratyphoid bacilli were negative on the fifth, seventh, eleventh, fifteenth, seventeenth and twenty-eighth days of the disease. In another case the typhoid and paratyphoid agglutination reactions, were all negative, until the 29th day when the blood gave a suspicious reaction. In one other case the same reactions were positive on the 19th and negative on the 25th and 30th day of the disease. In the other cases the reactions were negative throughout the course of the disease.

Continued Fevers Group D.

In addition to the fevers already described we had in Panama another very interesting group, represented by a series of eight cases. These fevers were caused by a group of bacilli quite distinct from any heretofore described. These bacilli are medium sized rods, actively motile, having peritrichic flagella, which are easily stained on very old cultures. The growth on agar slants is opalescent and bluish gray. The colonies on agar plates are round, moist, homogeneous and have an opalescent bluish gray appearance,

exactly like those of the typhoid bacillus. These organisms grow quite slowly in broth producing a light diffuse turbidity. In milk these bacilli produce a solid coagulation and cause after several days incucation some peptonization. Litmus milk is completely decolorised, but gradually turns pink. The growth in gelatin is abundant along the line of inoculation and on the surface a light bluish gray film is formed. The growth on potato is quite characteristic. It is abundant in quantity and pigmented, the pigment varying with the different members of the group from cream colored to a dark chocolate brown. These bacilli resemble very closely the typhoid bacillus in that they do not produce gas in glucose, lactose, saccharose, galactose, mannite, dextrine, sorbite, inulin, maltose, levulose, arabinose, raffinose, mannose, zylose, rhamnose, glycerin, salicin or melanyte. Acid is formed in glucose, lactose, saccharose, galactose, dextrine, levulose, mannose, zylose, and glycerin. These organisms grow very slowly onall medium. The typhoid and paratyphoid Widal reactions for this series of cases were negative. Still all of these bacilli were agglutinated by the patients own serum. These bacilli do not form indol. All of these organisms were pathogenic for guinea pigs

Clinical Symptoms.

This group of cases is thus represented by a series of organisms which is easily distinguished from any of the

preceding groups. The cases also show clinical features which separate them sharply from the other groups described. It is represented by eight cases which occurred within a period of six months. It is interesting to note that the temperature charts showed conditions ranging from afebrile to fairly severe continued fever. The majority of these cases may be characterised as low grade continued fever. A most remarkable and interesting feature in this series of cases is that the associated bacilli could be isolated from the blood as long as the patient was under observation. In this series of cases blood cultures were made every five days throughout the patient's illness and all proved positive even after the patients were convalescent. Some of these patients kindly permitted me to take blood cultures even after their discharge from the hospital and in a number of instances the organisms were still present in the blood stream three months later. An interesting fact concerning these cases is that at no time during the course of the disease are the patients so uncomfortable as are those suffering from other infections of a typhoid-like character. Another interesting feature seems to be that a much longer time is required for the effects of the fever to wear off and the patient regain normal health. The prolongation of these symptoms may bear some analogy to the persistency of the bacilli in the blood.

General Considerations Concerning the Organisms Isolated

Typhoid Bacillus.

The organisms originally isolated from the blood of enteric fever cases in Panama were brought back to America and have been submitted to painstaking study and comparison in the Bacteriological Laboratory of the Johns Hopkins University. In every instance the reactions observed in Panama were subsequently confirmed. The organisms isolated from the blood of enteric fevers in Panama and classified as typhoid bacilli may be characterised as follows: These bacilli are about three times as long as wide with rounded ends. They may appear at one time as very short ovals, at another time as long threads, and both of these forms may appear together. The breadth of these bacilli remains tolerably constant. The morphological characters, present but little that will aid in their identification. They stain a trifle less readily with the analine dyes than do most of the other organisms. These bacilli are actively motile and when stained by special methods beautiful hair-like flagella are observed which are attached in large numbers to all parts of the bacillus. These bacilli do not form spores, although irregularities of staining are often observed in these organisms, owing to a retraction of the protoplasm from the cell envelope which seem to produce vacuoles in the bacilli. This organism stains more or less irregularly. The colonies on agar plates possess no very typical characteristics. The colonies are round, homogeneous and bluish gray. The growth on agar slants is abundant, and has an opalescent bluish gray appearance. These organisms

give a light diffuse turbidity to broth cultures. In gelatin stab cultures the growth is mostly on the surface, there being only a limited development down the track made by the needle. The surface growth has the same general appearance as the colonies on the plates. These bacilli do not coagulate milk, litmus milk at first is neutral but after several hours incubation turns acid and remains acid. The growth on potato is usually luxuriant, but invisible, making its appearance evident only by the production of a slight increase of moisture along the line inoculated and by a limited resistance offered to aneedle when it is scraped across the tract of growth. While this is true in many cases, yet it cannot be considered as invariable, for at times this organism gives a more or less visible growth on potato. These bacilli fail to produce indol or reduce nitrites to nitrates. These organisms do not form gas in any of the carbohydrates, but do produce acid fermentation in glucose, galactose, mannite, maltose, levulose raffinose, mannose, zylose and glycerin. No acid changes are observed in lactose, saccharose, dextrine, sorbite, inulin, arabinose, rhamnose salicin and melanynite. The cultural and morphological characteristics of these bacilli are in every way identical with the bacillus described by Eberth, and Gaffky. As the typhoid bacillus, they isolated this organism from enteric fever cases and this organism was considered by them to be the etiological factor of the disease. These bacilli

described in this investigation were isolated from the blood of enteric fever cases, and since the cultural and morphological characters correspond exactly with the descriptions of the typhoid bacillus of Eberth and Gaffky they must be identical and be likewise considered as the cause of the typhoid fever in Panama.

Paratyphoid Bacillus I

The organisms isolated from the blood of these continued fevers are about three times as long as wide, the length however is somewhat variable, when grown on different medium. It may form very short rods or even long threads. This organism is actively motile, and has numerous lateral flagella. These organisms do not stain as well with the ordinary analine dyes as do most bacteria, and do not stain by Gram. Excellent bi-polar bodies are observed when the organisms have been grown on potato cultures. The growth on agar slants resembles the growth of the typhoid bacillus It has an opalescent bluish gray appearance. The colonies on agar are round, moist, with an opalescent bluish gray lustre. Broth cultures after 24 hours incubation show a light diffused turbidity. No sediment is observed even after several days. The growth in gelatin stabs is abundant along the line of inoculation.The surface growth presents an opalescent bluish-gray appearance. In litmus milk the culture remains unchanged at first, but after a few hours

incubation the milk becomes slightly acid and after a few days it turns alkaline, and remains alkaline, no coagulation takes place, although in old cultures the casein is dissolved. On potato the growth is slight and almost invisible. The indol, nitrite and phenol reactions were negative. These organisms were all pathogenic for guinea pigs. These organisms form gas and acid in the following carbohydrates, glucose, galactose, mannite, dextrine, sorbite, maltose, levulose, arabinose, raffinose rhamnose, Acid but no gas was formed in zylose. No acid or gas developed in lactose, saccharose, inulin, mannose, glycerin and salicin.

These organisms were isolated from the blood of enteric fever cases and they seem to be identical with an organism which was first isolated by Gwyn from the blood of a case presenting typhoid symptoms. Boycott, Wells, Schottmüller and many other investigators have isolated a similar organism from the blood of cases resembling enteric fever ~~cases~~, and it is believed by them, to be a cause of ~~enteric~~ the fever. It seems reasonable therefore to infer that these organisms which were isolated from the blood of ~~enteric~~ patients with this type of fever in Panama belong to this paratyphoid group type B and that they were the etiological factor in these cases.

Organisms From Group A.

The organisms which were isolated from the blood of patients with suspected enteric fever in this group of cases are good sized rods, three to five times as long as wide, with rounded ends,

the length varies greatly with the nature of the medium on which ~~it~~ they grow~~s~~, On agar the bacilli appear as very short rods, while on potato they may grow into long threads, and may give rise to involution forms.

These organisms are actively motile and have numerous lateral flagella. Terminal round oval bodies are found on potato and agar cultures which are grown in the incubator for several days. They do not double stain and the bacilli containing these plain bodies are very susceptible to heat; they are not therefore true spores, but rather little masses of condensed protoplasm. These bacilli are very resistant to dessication and may retain their vitality for months. These bacilli hesitate to stain by Gram's method, Excellent bipolar stains are observed when the organisms are grown on potato. The growth of this organism on artificial medi~~um~~a is less rapid than that of either the typhoid or the paratyphoid bacillus. Nevertheless the cultural properties of this group of organisms greatly resemble those of the typhoid and paratyphoid bacilli. In stroke cultures on agar there is a bluish gray film of growth, with fairly regular margin but without any characteristic features. This film is loosely attached to the surface and can be easily scraped off. On agar plates the surface colonies are round, moist, opalescent and bluish gray. In gelatin the growth is abundant along the

line of inoculation. The surface growth is much like the growth of the typhoid bacillus in forming a bluish gray film. Cultures in broth after 24 hours incubation have a uniform turbidity, without any apparent sedimentation. These organisms do not produce any visible change in litmus milk. The growth on potato is almost invisible. These bacilli do not form indol, or reduce nitrates. These organisms are pathogenic for guinea pigs. These bacilli, ~~are~~ so far as their morphology is concerned, cannot be differentiated from either of the two preceding groups of organisms. The growths on agar, gelatin, broth, are in every way identical with those of the typhoid and the paratyphoid bacilli. These organisms agree with the typhoid bacillus in their reactions on litmus milk, and differ from the paratyphoid bacillus in that the ~~paratyphoid bacilli~~ latter are at first neutral in litmus milk and then produce a strong alkalinity. The distinguishing feature of this group is its deportment ~~on~~ with the various carbohydrates. This organism splits the following sugars with the formation of both gas and acid glucose, saccharose, mannite, dextrine, arabinose, mannose, rhamnose and salicin. No changes are observed in lactose and inulin, acid but no gas is produced in galactose, sorbite, maltose, levulose, raffinose, glycerin and melanyte. Since these organisms produce gas in glucose, saccharose and mannite, etc., they cannot belong to the typhoid group and because they ferment saccharose and do not produce alkali in milk, they are

not to be considered among the paratyphoid bacilli type [illegible]. Since these organisms do not correspond to either of the two preceding groups, I have only described them for the present as continued fevers group A, and as far as I am aware these organisms have not heretofore been isolated from the blood of continued fevers. These organisms while they do not ferment glycerin are very likely identical with paratyphoid A.

Organisms from Group B.

The bacilli which were isolated from this group of fevers are about three times as long as wide and have rounded ends. Their morphological characters like those of the typhoid bacillus may show great variations, particularly in length. They may appear as short almost coccus-like bodies and at other times as long threads, like the typhoid bacillus. Both the long and short forms may develop in the same medium. These organisms are actively motile and possess peritrichic flagella; they are Gram-negative and do not form spores. The growth on agar slants forms a thin bluish gray film which covers the surface of the medium.

The colonies on agar are round, homogeneous and have an opalescent bluish gray appearance. These organisms impart a slight diffuse turbidity to the broth, and form very little sediment even in old cultures. The growth in gelatin stab is very abundant along the line of inoculation, and especially on the surface where it spreads as a thin, grayish white growth. In litmus milk these organisms

produce no visible change, the color remains unchanged even after 15 days of incubation. The growth on potato, while quite abundant, remains about the color of the medium. On the various carbohydrates some very interesting differences are to be noted. The sugar reactions take place very slowly but after five days incubation both acid and gas are produced in galactose, mannite, dextrine, maltose, levulose and dulcite. In addition to these changes acid fermentation is observed in glucose, lactose, sorbite arabinose, raffinose, levulose, rhamnose, melanyte and glycerin. The indol reaction is negative, these organisms do not reduce nitrites to nitrates. The patient's serum was not agglutinated by the typhoid or paratyphoid bacillus within the 28th day of the disease.

This group of organisms differs from the typhoid bacillus in the production of gas in galactose, mannite, dextrine, maltose and levulose. They differ from the paratyphoid bacillus in that no gas is formed in glucose, and that milk cultures remain unchanged. Whereas the paratyphoid bacillus B at first either leaves the litmus milk unchanged or slightly acid but later the litmus milk is turned strongly alkaline.

The reaction in litmus milk corresponds with the paratyphoid bacillus group A, ~~but differs in its ability to form gas in glucose and saccharose.~~ As far as I know this

is the first time an organism with the above characteristics has been described as having been isolated from the blood of ~~enteric~~ patients affected with typhoid or typhoid-like fevers.

Organisms from Group C.

The organisms representing this group were obtained from the blood of eight cases of continued fevers. These bacilli are short rods about three times as long as broad. They are actively motile with peritrichic flagella. They do not retain the stain when treated by Gram's method. The cells do not take the stain uniformly and the vacant cavities might be taken as vacuoles or metachromatic granules. These bacilli form on agar slants a moist, white, spreading growth which is much more abundant than the growth of the typhoid bacillus. The colonies on agar are round, homogeneous and slightly opalescent. The broth cultures show a very heavy cloudy turbidity. In gelatin stabs they produce a rather energetic growth along the line of inoculation while on the surface it spreads as a white moist film. Litmus milk shows no change even after 10 days of incubation. The growth on potato at first is almost invisible, but after five or six days a faint lemon yellow growth is observed. Two of these strains gave a faint indol reaction, while the other two were negative. None of these organisms reduce nitrites to nitrates and no indol is formed. The agglutination reactions, using typhoid

and paratyphoid bacilli against the patient's serum all were negative. These organisms are pathogenic for guinea pigs. This group of bacilli ferment the following carbohydrates with the production of both gas and acid; glucose, lactose, galactose, mannite, maltose, levulose, arabinose, raffinose, rhamnose and salicin, acid but no gas is formed in glycerin. These organisms do not form acid or gas in saccharose, dextrine, sorbite, inulin, mannose and dulcite.

The cultural characters of the organism are quite distinct from those already described. In many ways they are closely related to *Bacillus coli*. Morphologically they are not unlike the bacillus of Escherich. The colonies on agar plates, the growths on agar slants, the growths in broth and in gelatin are identical with those of the colon bacillus. These organisms do not coagulate milk, neither do they produce any changes in litmus milk, even after long incubation.* On potato at first the growth is almost invisible, but after five or six days, a faint lemon yellow growth is observed. Two of these strains gave a faint indol reaction, while the other strains were negative. None of these strains reduce nitrates to nitrites, and no phenol is formed. These organisms are more closely related to the bacillus coli of Escherich than to any of the other group, associated with continued fevers, and I can find no record where such organisms have been isolated from the blood in enteric

* The behavior of the organism in milk seems for the present irreconcilable with the fermentation of lactose. Since completion of the investigation the question has been raised whether for some unexplained reason the bacillus failed to grow in the milk.

fevers but there can be no doubt but that they were the etiological factors in the causation of this group of enteric fevers.

Organisms from Group D.

The organisms isolated from this group of enteric fever cases, are good sized rods, three to five times as long as wide with rounded ends, The length varies greatly with the composition of the medium on which the organisms are grown. On agar the rods are very short while on potato involution forms may occur. These bacilli are very actively motile but if grown for a long time on artificial media they may show little or no motility. These organisms have peritrichic flagella. These bacilli are Gram negative, and they show beautiful bi-polar stains when grown on potato. These bacilli grow on agar slants ~~and~~ very much like the typhoid bacillus, the surface presents a moist bluish-gray appearance.The colonies on agar are medium sized, round, moist, opalescent and bluish gray. In broth the growth is light and diffused giving a light cloudiness to the medium. The growth in gelatin stab is abundant along the line of inoculation and on the surface with no liquefaction. Milk cultures at the end of 24 hours incubation shows little or no change but if the incubation be continued for five days a soft curd forms, and the litmus milk is

completely decolorised and after about five days incubation the milk becomes coagulated. The milk thus coagulated after about two weeks, undergoes a slight peptonization. The growth on potato is very abundant and forms a pigment which varies with the different members of the group some of these bacilli produce a cream, some lemon yellows and even a chocolate brown pigment has been observed. These bacilli do not form indol, phenol or reduce nitrites to nitrates. These bacilli are pathogenic for guinea pigs. These organisms do not produce gas in any of the carbohydrates but form acid in glucose, lactose, saccharose, galactose, dextrine, levulose, mannose, zylose and glycerin. The representatives of this group of enteric fevers resemble very closely the bacillus of Eberth, and their behavior on the various carbohydrates is very similar. They differ chiefly because these organisms coagulate milk and likewise produce a heavy pigmented growth on potato. These bacilli resemble the bacillus coli only with regard to their ability to coagulate milk. These organisms are quite distinct from any of the groups previously described, and seem to belong in a class by themselves.

Castellani has isolated a somewhat similar organism from the blood in two cases of continued fevers. The bacilli which he isolated are described as non-motile, Gram negative and corresponding in every respect to the

morphology of the typhoid bacillus. The cultural characteristics were identical with the typhoid bacillus with the exception of the coagulation of milk and the absence of motility. These bacilli seem to differ from the Panama organisms only in the question of motility. I have been unable to obtain a culture of Castellani's organism, so I have been unable to compare the two organisms.

CONCLUSIONS.

This series of investigations leads to the following conclusions:

1. Continued fevers in Panama may be caused by a great variety of organisms other than the typhoid bacillus and these organisms are present in the blood during the first ten or twelve days of illness or within the first ten or twelve days of a relapse.

2. There are certain types of organisms giving rise to continued fevers which produce more serious conditions than others and the prognosis varies accordingly.

3. Systematic blood cultures serve as the only reliable means of diagnosing continued fevers, and without blood cultures a large percentage of these would escape a correct diagnosis.

4. Our results indicate that in Panama about one-fourth (24%) of the cases of fevers called typhoid is caused by the paratyphoid bacillus type B. If we group together the paratyphoid cases, and the cases of continued fevers Groups A, B, C, and D we find that about 57% of all clinical typhoids are caused by organisms other than the typhoid bacillus.

5. In typhoid fever in Panama there were 13% of relapses, with a total mortality of 14%. Among the para-

typhoid fevers we find that 46% of the cases had definite relapses yet the total mortality was only 4%. In group A of the continued fevers which had a mortality of 38% there were no relapses. In group B while there were no relapses the mortality was 16%. In groups C and D we find no relapses and we have a mortality of 25%.

6. The proportion of continued fevers which is caused by organisms other than the typhoid bacillus seems to be very much greater than is generally supposed. It is possible that the proportion of paratyphoid and closely allied fevers which has been observed in Panama likewise exists in Northern Climates.

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In the following tables are recorded the morphological and cultural reactions of the organisms isolated from continued fevers in Panama and one of the tables represents the cultural and morphological characters of the intermediate group.

Table I Represents the typhoid bacillus
Table 2 " slight variations of the typhoid bacillus
Table 3 " some organisms of the intermediate group.
Table 4 " Paratyphoid bacillus.
Table 5 " Continued fevers Group A.
Table 6 " " " " B
Table 7 " " " " C
Table 8 " " " " D.

Explanation of Tables

SR = Short Rod
+, motility, presence of flagella, stained by gram, presence of indol agglutination, specific agglutination and pathogenicity, neg. sign negative results.
L D., light diffused turbidity,
+ no coagulation of milk
+
+ coagulation of milk
− acidity of milk
=, no production of gas in the carbohydrate medium
+, " production of acid " " " " "
+, " " gas " " " " "
" " " acid " " " " "
−, no gas
TR trace of red decolorization of the litmus carbohydrate medium
LR. light red " " " " " "
VLR. Very light red " " " " " "
LTR light shade of red " " " " " "
R = red " " " " " " "
+ gas in carbohydrate medium

FOLD OUT

The following temperature charts represent only the maximum and minimum ranges of temperature in each group of enteric fevers.

Charts 1 and 2 ------------------ Typhoid fever.
" 3, 4 and 5 --------------- Paratyphoid fever
" 6 and 7 ---------------- Continued fevers A.
" 8 and 9 ---------------- " " B
" 10 and 12 --------------- " " C
" 12, 13, 14 --------------- " " D.

FOLD OUT

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